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Electrochemical Deallylation of α-Allyl Cyclic Amines and Synthesis of Optically Active Quaternary Cyclic Amino Acids

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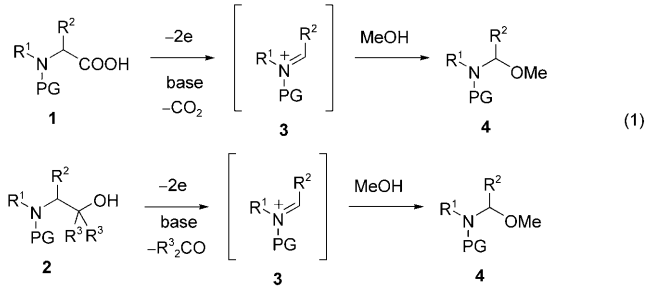
Abstract: Electrochemical oxidation of α-allylated and α-benzylated *N*-acylated cyclic amines by using a graphite anode easily affords the corresponding α-methoxylated products with up to 76% yield. Ease of oxidation was affected by the type of electrode, the size of cyclic amine, and the nature of the protecting group. This method was successfully applied to the synthesis of optically active *N*-acylated α-alkyl-α-amino acid esters with up to 99% *ee*.

Keywords: alkylation · allylation · amino acids · diastereoselectivity · electrochemical oxidation

Introduction

Electrochemical oxidation of *N*-acyl-α-amino acids **1** or *N*-acyl-β-hydroxyl amines **2** in methanol has already been reported to afford α-methoxylated amines **4** via acyliminium ion intermediates **3** [Eq. (1)].[1]



(1)

These α-methoxylated compounds **4** have been utilized as starting materials in the synthesis of cyclic lactams,[2] alkaloids,[3] *d-threo*-methylphenidate,[4] and even the antimalarial agent, isofebrifugine.[5] We report for the first time electrochemical deallylation and debenzylation of *N*-acyl-α-allylated and α-benzylated cyclic amines. We have also successfully applied this method to the synthesis of optically active quaternary amino acid esters with up to 99% enantiomeric excess (*ee*).

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Results and Discussion

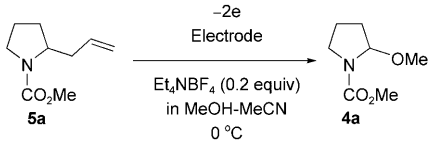
Anodic deallylation: Initially we studied the electrochemical deallylation of α-allyl-*N*-acyl cyclic amines. Several α-allyl cyclic amines **5a–j** were synthesized and subjected to electrochemical deallylation. Our initial investigation began with finding suitable electrodes from platinum, glassy carbon, and graphite capable of supporting the electrochemical oxidation of α-allyl-*N*-methoxycarbonylpyrrolidine (**5a**) as a model substrate.

We observed that when the platinum anode was paired with a graphite cathode, deallylated derivative α-methoxy-*N*-methoxycarbonylpyrrolidine (**4a**) was obtained in a better yield relative to the glassy carbon and platinum cathodes (Table 1, entries 1–3). On the other hand, the glassy carbon anode demanded relatively high electric loading and afforded almost the same yields with any cathodes (entries 4–6). The graphite anode required relatively less electricity and gave an optimum yield of **4a** when paired with the platinum cathode (entries 7–9).

Tetraethylammonium *p*-toluenesulfonate (Et_4NOTs) as a supporting electrolyte did not improve this reaction (Table 1, entry 10). The optimized reaction conditions were applicable to the anodic deallylation of some α-allyl-*N*-acylated amines **5a–k** (Table 2).

Relatively bigger α-allylated cyclic amines were then investigated. Deallylation of α-allyl-*N*-methoxycarbonylpiperidine (**5b**) proceeded with 72% yield to give the corresponding α-methoxy-*N*-methoxycarbonylpiperidine (**4b**) (Table 2,

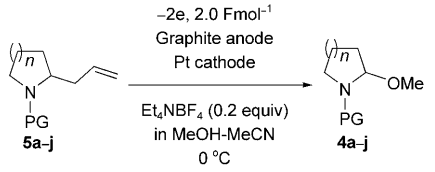
Table 1. Determination of electrodes for the deallylation of α-allyl-*N*-methoxycarbonylpyrrolidine (**5a**).[a]

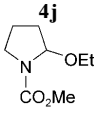


Entry	Electrode		Electricity	Yield
	Anode	cathode	[F mol^{-1}]	**4a** [%]
1	platinum	platinum	2.5	51
2	platinum	glassy carbon	3.0	47
3	platinum	graphite	2.5	56
4	glassy carbon	glassy carbon	3.0	53
5	glassy carbon	platinum	3.0	48
6	glassy carbon	graphite	3.0	51
7	graphite	graphite	2.0	52
8	graphite	glassy carbon	3.0	51
9	graphite	platinum	2.0	68
10[b]	graphite	platinum	3.0	36

[a] The substrate **5a** (0.5 mmol) and Et_4NBF_4 (0.1 mmol) were placed in a beaker-type cell containing a stirring bar. Methanol (2 mL) and acetonitrile (8 mL) were added and the mixture was stirred at 0 °C. The electrodes were fitted and appropriate electricity was passed through. [b] Et_4NOTs (0.5 equiv) was used as a supporting electrolyte.

Table 2. Anodic deallylation of α-allyl-*N*-acylated amines **5a–j**.[a]

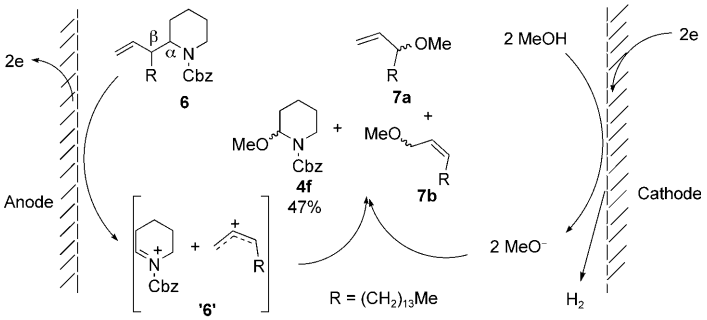


Entry	PG	*n*	Substrate	Product	Yield [%]
1	CO_2Me	1	**5a**	**4a**	68
2	CO_2Me	2	**5b**	**4b**	72
3	CO_2Me	3	**5c**	**4c**	66
4	CO_2Me	4	**5d**	**4d**	70
5	CO_2CH_2Ph	1	**5e**	**4e**	70
6	CO_2CH_2Ph	2	**5f**	**4f**	76
7	CO_2CH_2Ph	3	**5g**	**4g**	61
8	CO_2CH_2Ph	4	**5h**	**4h**	64
9	COPh	1	**5i**	**4i**	65
10	COPh	3	**5j**	**4j**	69
11[b]	CO_2Me	1	**5a**	 **4k**	51

[a] The substrates **5a–j** (0.5 mmol) and Et_4NBF_4 (0.1 mmol) were placed in a beaker-type cell containing a stirring bar. Methanol (2 mL) and acetonitrile (8 mL) were added and the mixture was stirred at 0 °C. The graphite anode and platinum cathode were fitted and 2.0 F mol^{-1} of electricity was passed through. [b] Ethanol (2 mL) and acetonitrile (8 mL) were added and the mixture was stirred at 0 °C.

entry 2). Further, α-allyl-*N*-methoxycarbonylazepane (**5c**) and α-allyl-*N*-methoxycarbonylazocane (**5d**) led to the corresponding α-methoxylated compounds **4c** and **4d** with good yields, respectively (entries 3 and 4). A change of *N*-acyl groups was tolerated. For instance, α-allyl-*N*-benzyloxycarbonylpyrrolidine (**5e**) gave the desired product albeit with a slightly improved yield relative to *N*-methoxycarbonylated pyrrolidine **5a** (entries 1 and 5). In addition, α-allyl-*N*-benzyloxycarbonylpiperidine (**5f**), α-allyl-*N*-benzyloxycarbonylazepane (**5g**), and α-allyl-*N*-benzyloxycarbonylazocane (**5h**) efficiently yielded the corresponding α-methoxylated compounds, **4f–h** (entries 6–8). Finally, α-allyl-*N*-benzoylpyrrolidine (**5i**) and α-allyl-*N*-benzoylazepane (**5j**), as expected, furnished the corresponding α-methoxylated compounds **4i** and **4j** in appreciable yields (entries 9 and 10). A change of solvent to EtOH/MeCN though low yielding gave the anticipated α-ethoxylated compound **4k** (entry 11).

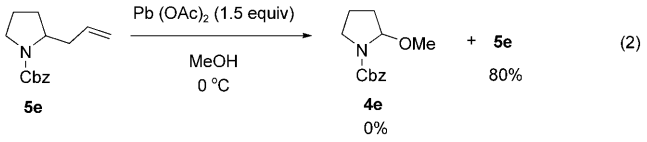
Deallylation mechanism: Initially, we determined whether the reaction intermediate was a radical species, by carrying out deallylation of α-allyl-*N*-methoxycarbonylpyrrolidine (**5a**) with a large excess (10 equiv) of butyl acrylate as a free-radical scavenging additive. The reaction proceeded smoothly to yield the expected α-methoxylated pyrrolidine **4a** and butyl acrylate was recovered. This result implied that the reaction did not proceed through an allyl radical, but probably through an allyl cationic intermediate. To test the feasibility of such a hypothesis, we prepared α-(1-myristylallyl)-*N*-benzyloxycarbonylpiperidine (**6**) with (2-heptadecenyl)trimethylsilane[6] and carried out electrochemical deallylation. A plausible reaction pathway based on the observed results is outlined in Scheme 1. We propose that



Scheme 1. Plausible electrochemical deallylation route.

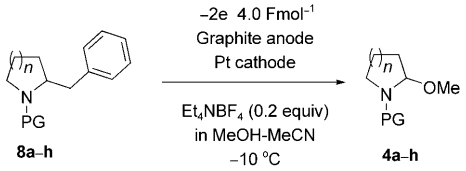
under a constant electrical current, electron absorption takes place at the anode, which brings about the carbon–carbon (C–C) bond cleavage between the α and β carbon atoms to generate an acyliminium ion and allylic cation **'6'** (Scheme 1)[7] similar to those anodically generated from amino acids and alcohols.[1] These ions are then trapped with nucleophiles, such as methoxide, to afford 47% of α-methoxy cyclic amine **4f**. The methyl ether **7a** and its regioisomer **7b** as side products (sum up ~80% yield) were detected by GCMS confirming this hypothesis.

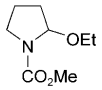
Chemical deallylation: We unsuccessfully attempted to carry out chemical deallylation by using lead(IV) acetate[8] in methanol at 0 °C [Eq. (2)].



Anodic debenzylation: α-Benzyl-*N*-acyl cyclic amines **8a–h** were then investigated. Electrochemical oxidation of α-benzyl-*N*-methoxycarbonylpyrrolidine (**8a**) afforded α-methoxylated product **4a** in 67% yield. The reaction required a low temperature, −10°C (Table 3, entries 1 and 2), and a high electric loading (4 F mol^{-1}) for optimum yield.

Table 3. Anodic debenzylation of α-benzyl-*N*-protected amines **8a–h**.[a]

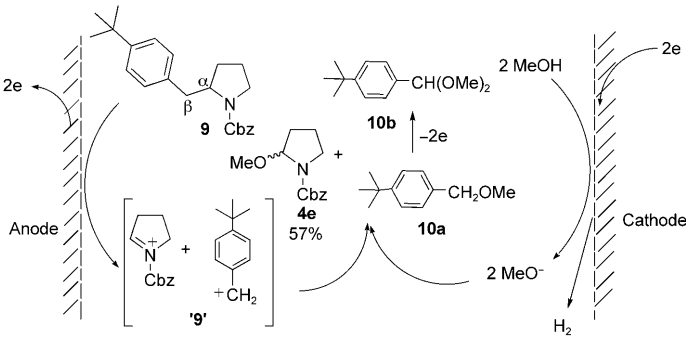


Entry	PG	*n*	Substrate	Product	Yield [%]
1	CO_2Me	1	**8a**	**4a**	67
2[b]	CO_2Me	1	**8a**	**4a**	57
3	CO_2Me	2	**8b**	**4b**	62
4	CO_2Me	3	**8c**	**4c**	66
5	CO_2Me	4	**8d**	**4d**	71
6	CO_2CH_2Ph	1	**8e**	**4e**	57
7	CO_2CH_2Ph	2	**8f**	**4f**	65
8	CO_2CH_2Ph	3	**8g**	**4g**	72
9	CO_2CH_2Ph	4	**8h**	**4h**	74
10[c]	CO_2Me	1	**8a**	 **4k**	47

[a] The substrate (0.5 mmol) and Et_4NBF_4 (0.1 mmol) were placed in a beaker-type cell containing a stirring bar. Methanol (2 mL) and acetonitrile (8 mL) were added and the mixture was stirred at −10°C. The graphite anode and platinum cathode were fitted and 4.0 F mol^{-1} of electricity was passed through. [b] The reaction was carried out at 0°C. [c] Ethanol (2 mL) and acetonitrile (8 mL) were added and the mixture was stirred at −10°C.

Debenzylation of α-benzyl-*N*-methoxycarbonylpiperidine (**8b**) proceeded smoothly, yielding the corresponding α-methoxypiperidine **4b** (Table 3, entry 3). Similarly, debenzylation of α-benzyl-*N*-methoxycarbonylazepane (**8c**) and α-benzyl-*N*-methoxycarbonylazocane (**8d**) proceeded with good yields, 66 and 71%, respectively (entries 4 and 5). A change of *N*-acyl group was well tolerated. For instance, α-benzyl-*N*-benzyloxycarbonylpyrrolidine (**8e**) yielded its corresponding α-methoxypyrrolidine **4e** in average yield (entry 6). Bigger α-benzyl-*N*-benzyloxycarbonyl cyclic amines **8f–h** underwent anodic cleavage with improved yields, 65, 72, and 74%, for α-methoxypiperidine **4f**, α-methoxyazepane **4g**, and α-methoxyazocane **4h**, respectively (entries 7–9). A change of solvent to EtOH/MeCN gave the anticipated α-ethoxylated compound **4k** (entry 10) albeit in a low yield.

Debenzylation mechanism: Electrochemical oxidation of α-(4-*tert*-butyl)benzyl-*N*-benzyloxycarbonylpyrrolidine (**9**) proceeded smoothly to yield the corresponding α-methoxypyrrolidine **4e** and a mixture of *p*-methoxymethyl-*tert*-butylbenzene (**10a**)[9] and *p*-dimethoxymethyl-*tert*-butylbenzene (**10b**).[9] This implies that under a constant electrical current, absorption of electrons takes place at the anode, which brings about the carbon–carbon (C–C) bond cleavage between the α and β carbon atoms to generate the acyliminium ion and benzylic cation **'9'** similar to those anodically generated during electrochemical deallylation (Scheme 2). The acyliminium ion is then trapped with methoxide to afford 57% of α-methoxylated cyclic amine **4e**. Similarly, trapping of a benzylic cation with methoxide afforded methyl ether **10a** and dimethyl acetal **10b**, generated by further oxidation of **10a**, isolated as side products (sum up ~71% yield).

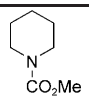
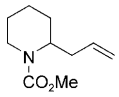
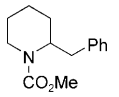
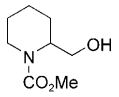


Scheme 2. Plausible electrochemical debenzylation route.

Oxidation potentials: Oxidation peak potentials of four cyclic amines were measured by cyclic voltammetry. The results are shown in Table 4. The most oxidizable compound as expected was nonsubstituted *N*-methoxycarbonyl amine **11** (entry 1), whereas α-hydroxymethylated amine **12** was hardly oxidizable (entry 4). The amine with an α-allyl substituent (**5a**, entry 2) was more oxidizable than that with a α-benzyl substituent (**8a**, entry 3).

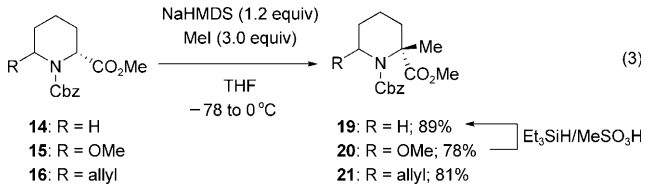
Synthetic application to optically active quaternary cyclic amines via α-allylated intermediates: In view of the biological importance of optically active α-alkyl-α-amino acids,[10] several synthetic methods have been reported.[11] However, the development of new methods with the use of easily available starting materials and convenient procedures is still very important. We have previously demonstrated Shono-type α′-allylation of amino acids.[12] In this study, diastereoselective α′-allylation of methyl 6-methoxy-*N*-benzyloxycarbonyl-D-pipecolinate (**15**) derived from D-pipecolinate **13** was carried out after *N*-acylation and electrochemi-

Table 4. Oxidation peak potentials observed by cyclic voltammetry.

Entry	Substrate	Oxidation potential [V][a]
1	 **11**	1.7
2	 **5a**	2.0
3	 **8a**	2.4
4	 **12**	>3.0

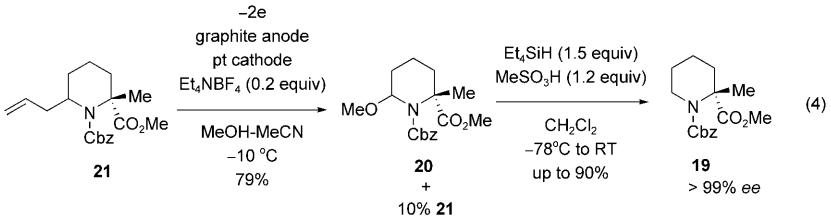
[a] Cyclic voltammograms were recorded on each substrate solution (10 mM) in MeCN containing Et_4NBF_4 (0.1 M): Glassy carbon disk as a working electrode 1.6 mm); scan rate = 0.05 $V s^{-1}$; $Ag/AgNO_3$ as a reference electrode.

α′-Allylated compound **16** underwent α-methylation after treatment with 1.2 equivalents of sodium hexamethyldisilazide (NaHMDS) and three equivalents of methyl iodide at −78 °C in THF to afford α′-allyl-α-methyl-α-amino acid ester **21** [Eq. (3)]. Removal of the α′-allyl auxiliary from **21** was accomplished by using two steps involving electrochemical deallylation at 5 $F mol^{-1}$ in methanol by using a graphite anode followed by methoxy-group cleavage with Et_3SiH and $MeSO_3H$ to afford methyl *N*-benzyloxycarbonyl-(2*R*)-methylpipecolinate (**19**) with >99 % *ee* [Eq. (4)]. Solvent and base effects on α-methylation of **16** were then determined (Table 5).



(3)

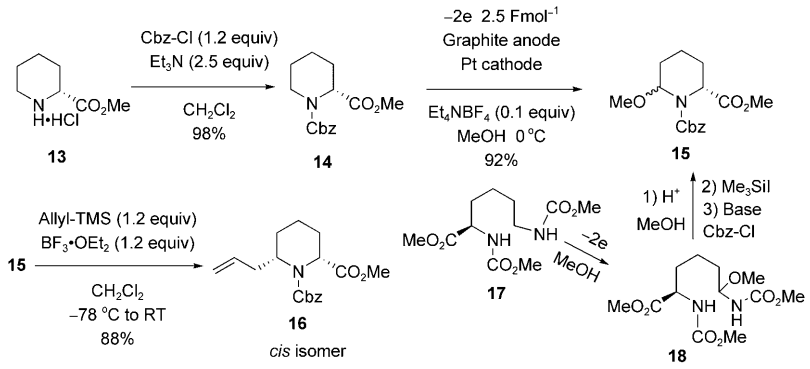
cal oxidation (Scheme 3). Compound **15** could also be inexpensively obtained from D-lysine-derivative **17** via **18** by electrochemical oxidation.[12b] Methyl (6*S*)-allyl-*N*-benzyloxycarbonyl-D-pipecolinate (**16**) was obtained from **15** after treatment with allyltrimethylsilane in the presence of a Lewis acid as a single *cis* isomer in excellent yield.



(4)

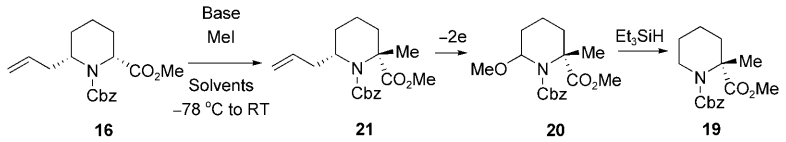
The direct introduction of an alkyl group to *N*-benzyloxycarbonyl-D-pipecolinate (**14**) at the α-position afforded *N*-benzyloxycarbonyl-α-methylpipecolinate **19** as a racemic mixture.[13] Further, **19** obtained from the alkylation of **15** followed by acidic cleaveage of the methoxy group was racemic [Eq. (3)]. In our preliminary study, we sought to achieve asymmetric induction through the use of an α′-allyl group.

Similar levels of enantioselectivity were obtained regardless of the base used (Table 5). Toluene and THF gave high yields for α-methylation and >99 % *ee* (entries 1 and 6). NaHMDS and potassium hexamethyldisilazide (KHMDS) gave good yields, whereas lithium diisopropylamide (LDA) and lithium hexamethyldisilazane (LiHMDS) gave moderate yields (entries 1–4). The reaction carried out from −60 °C gave a lower yield (entry 5). Dimethyl formamide (DMF) gave a moderate yield, but low enantiomeric excess (entry 7). DMF undergoes decomposition with strong bases, such as NaHMDS, and the decomposition products may have hampered the reaction.[15] Benzene was a poor solvent for this reaction. Even though it gave high enantiomeric excess, the yield was poor (entry 8). This may be due to the possibility that since the reaction was carried out at room temperature, the intermediates formed after the addition of the base were unstable and may have disinte-



Scheme 3. Preparation of methyl (6*S*)-allyl-*N*-benzyloxycarbonyl-D-pipecolinate (**16**).

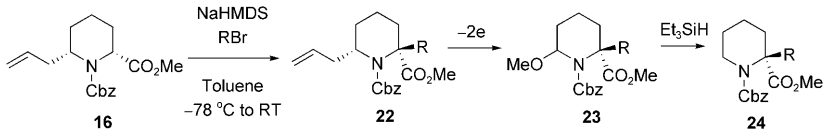
Table 5. Solvent and base effects on the α-methylation of **16**.[a]



Entry	Solvent	Base	Yield [%]			*ee* [%] of **19**[c]
			21	**20**[b]	**19**	
1	toluene	NaHMDS	88	77	87	>99
2	toluene	LDA	56	74	85	>99
3	toluene	KHMDS	85	76	84	>99
4	toluene	LiHMDS	69	73	80	>99
5	toluene	NaHMDS	77	78	89	>99
6	THF	NaHMDS	81	79	90	>99
7	DMF	NaHMDS	57	67	80	19
8	benzene	NaHMDS	23	69	72	>99
9	THF[d]	NaHMDS	78	66	69	>99

[a] Other than benzene (RT), DMF (from −60 °C), and entry 5 (from −60 °C), all other reactions were carried out from −78 °C. [b] Electrochemical oxidation was carried out in methanol by using a graphite anode and platinum cathode. [c] *ee* was determined by using a Daicel chiralcel OJ column (254 nm) and the absolute configuration was assigned by comparison of the specific rotation to the literature value, see: ref. [14]. [d] Other than THF containing the base, no other solvent was added.

Table 6. α-Alkylation of **16**.



Entry	R	Yield [%]						*ee* [%] of **24**[b]
		22		**23**[a]		**24**		
1[c]	Et	**22a**	79	**23a**	79	**24a**	87	>99 (*R*)
2	Et	**22a**	78	**23a**	76	**24a**	89	>99 (*R*)
3	allyl	**22b**	76	**23b**	70	**24b**	85	>99 (*R*)
4	2-propynyl	**22c**	80	**23c**	80	**24c**	84	75 (*R*)
5	propyl	**22d**	0	–	–	–	–	–
6	2-butenyl	**22e**	79	**23e**	trace[d]	**24e**	–	n.d.[e]
7	2-butynyl	**22f**	73	**23f**	trace[d]	**24f**	–	n.d.[e]
8	butyl	**22g**	0	–	–	–	–	–
9[f]	Me	**22h**	77	**23h**	80	**24h**	79	97[g] (*R*)

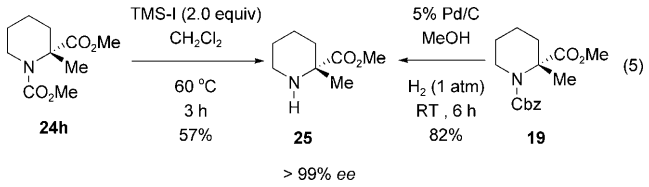
[a] Electrochemical oxidation was carried out in methanol by using a graphite anode and platinum cathode. [b] *ee* was determined by using a Daicel chiralcel OJ column (254 nm) and the absolute configuration was deduced on the basis of retention of configuration as observed in compound **19**. [c] EtI was used. [d] Reaction hardly proceeded and decomposition of the starting material was observed. [e] Not determined. [f] α′-Allyl-*N*-methoxycarbonyl-D-pipecolinate (**16h**) was used instead of **16** as a starting substrate. [g] *ee* was determined by using chiral GC.

EtBr had little effect (entry 2). In addition, an allyl group was also tolerated and yielded the desired α-allyl product **24b** in 85% yield and with >99% *ee* (entry 3). In the case of propynyl bromide, the alkylating reaction gave the desired product **22c** in a high yield, which underwent electrochemical deallylation and chemical demethoxylation to yield methyl *N*-benzyloxycarbonyl-(2*S*)-(2-propynyl)-pipecolinate **24c** with 75% *ee* (entry 4). Surprisingly, any attempts to introduce a propyl group at the α-position were futile (entry 5). Even though the 2-butenyl and 2-butynyl group were easily introduced at the α-position of **16** to yield **22d** and **22e**, respectively, consequent deallylation hardly proceeded (entries 6 and 7). As observed in the case of the propyl group, any attempts to introduce a butyl group failed (entry 8). Methyl (6*S*)-allyl-*N*-methoxycarbonyl-D-pipecolinate (**16h**) was prepared according to our recently reported method.[12b] This compound underwent α-alkylation, deallylation, and consequent demethoxylation to yield the quaternary amino acid **24h** in up to 79% yield and with 97% *ee* (entry 9). Removal of the *N*-acyl groups from the quaternary amino acid esters **19** and **24h** yielded amine **25** with >99% *ee* [Eq. (5)].

grated. When the reaction was carried out with only THF containing the base, the reaction cleanly afforded the desired product with a high yield and >99% *ee* (entry 9).

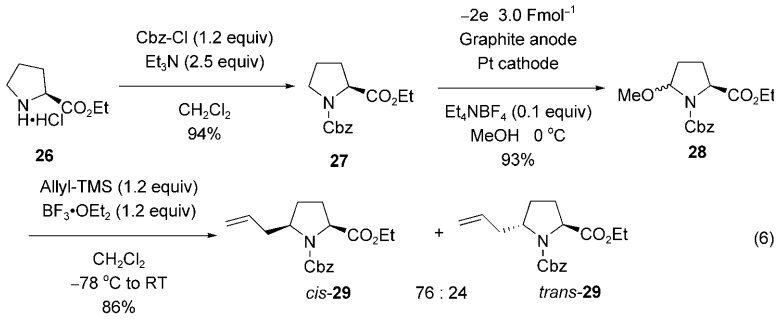
With regard to substrate scope, selected alkyl substituents were investigated (Table 6).

To our delight, we successfully introduced other alkyl substituents with good yields and enantioselectivities. For instance, an ethyl group was introduced at the α-position of **16** in up to 79% yield. The electrochemical removal of the α′-allyl group followed by demethoxylation of **23a** gave the desired quaternary amino acid ester, methyl *N*-benzyloxycarbonyl-(2*R*)-ethylpipecolinate (**24a**) with >99% *ee* (Table 6, entry 1). A change of the alkylating reagent from EtI to



Lastly, we attempted the preparation of α-alkylated L-proline. Diastereoselective α′-allylation of ethyl 5-methoxy-*N*-benzyloxycarbonyl-L-prolinate (**28**)[16] derived from **27** through *N*-acylation and electrochemical oxidation of **26**

gave two diastereomers **29** with the *cis* isomer as the major product in high yield [Eq. (6)].

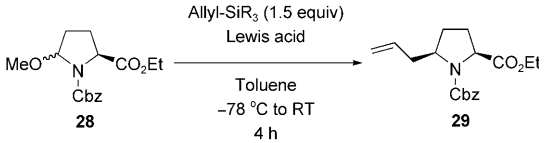


Attempts were made to improve the diastereoselectivity of compound **29** through the careful tuning of the reaction parameters: Lewis acids, allylating agents, solvents, and temperature (Table 7).

The allylation reaction with BF_3•OEt_2 and allyltrimethylsilane (allyl-TMS) gave **29** in 86% yield and with 42% diastereomeric excess (*de*; Table 7, entry 1). The use of allyltriisopropylsilane (allyl-TiPS) and a catalytic amount (20%) of triisopropylsilyl trifluoromethanesulfonate (TiPSOTf) improved the diastereomeric excess (entry 2). Dichloromethane was found to be unfavourable (entry 3). An increase of the catalyst loading to 60% somewhat improved the yield and diastereoselectivity (entry 4). The use of bulkier allyltriphenylsilane or allyltripentafluorophenylsilane[17] resulted in decreased yields (entries 5 and 6). Further tuning of the catalyst loading, temperature, and reaction time improved the diastereoselectivity with lower yields (entry 8). Interestingly, a change of Lewis acid to BF_3•OEt_2 leading to low selectivity gave an unexpected inversion of the stereoselectivity (entry 10). The reaction in entry 4 gave the best result and was selected for optimization of the solvent (Table 8).

Nonpolar solvents, fluorobenzene (PhF), benzene, xylene, toluene, and chloroform, gave the desired compound **29** with moderate to good *de* (Table 8, entries 1–5). The use of polar aprotic solvents gave mixed results. While ethyl acetate, ether, and THF had good to moderate selectivities, acetonitrile had poor selectivity (entries 6–9). The reaction from −78 °C to room temperature in toluene improved the diastereoselectivity with a moderate yield (entry 11). However, low selectivities were obtained in ether or fluorobenzene from −78 to 0 °C (entries 10 and 12). Trimethylsilyltrifluoromethanesulfonate (TMSTFMS) as a Lewis acid did not improve results (entries 13–15). The reaction in toluene from −78 to 0 °C improved selectivity to 94% though a low yield was obtained (entry 16). However, the reaction from −78 to 0 °C overnight dramatically improved the yield to 65% (entry 17). Attempts to improve this result by the use of two equivalents of Lewis acid or maintaining the reaction at 0 °C for longer periods were unsuccessful (entries 18–19). Conse-

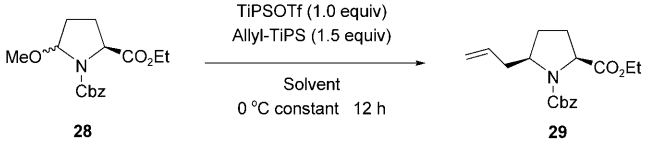
Table 7. Diastereoselective α′-allylation of ethyl 5-methoxy-*N*-benzyloxycarbonyl-L-prolinate (**28**).



Entry	Lewis acid [equiv]	R	**29** yield [%]	*de*[a] [%]
1	BF_3•OEt_2 (1.2)	Me	86	42
2	TiPSOTf (0.3)	*i*Pr	60	82
3[b]	TiPSOTf (0.3)	*i*Pr	53	68
4	TiPSOTf (0.6)	*i*Pr	62	83
5	TiPSOTf (0.6)	Ph	41	91
6	TiPSOTf (0.6)	PhF_5	trace	–
7[c]	TiPSOTf (0.1)	*i*Pr	47	89
8[c,d]	TiPSOTf (0.3)	*i*Pr	30	91
9[c,d]	TiPSOTf (0.1)	*i*Pr	30	76
10[d,e]	BF_3•OEt_2 (1.0)	*i*Pr	45	−38[f]

[a] Determined by using a Daicel chiralpak AD column (254 nm). [b] Reaction was carried out in dichloromethane. [c] Reaction was carried out at constant temperature of 0 °C. [d] Reaction was carried out for 36 h. [e] Reaction was carried out from 0 °C. [f] *trans*-**29** was the major isomer.

Table 8. Optimization of the diastereoselective α′-allylation of **28**.



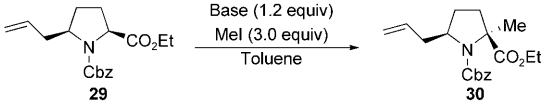
Entry	Solvent	*T* [°C]	*t* [h]	**29** yield [%]	*de* [%]
1	PhF	0	12	55	84
2	benzene	RT	12	56	62
3	xylene	RT	12	50	60
4	toluene	0	12	54	81
5	$CHCl_3$	0	12	35	74
6	AcOEt	0	12	46	66
7	MeCN	0	12	52	32
8	THF	0	12	38	64
9	ether	0	12	42	85
10	ether	−78 to RT	12	36	79
11	toluene	−78 to RT	12	50	92
12	PhF	−78 to RT	12	47	82
13[a]	ether	−78 to RT	12	46	62
14[a]	toluene	−78 to RT	12	52	78
15[a]	PhF	−78 to RT	12	48	72
16	toluene	−78 to 0	5	35	94
17	toluene	−78 to 0	12	65	94
18[b]	toluene	−78 to 0	5	53	90
19	toluene	−78 to 0	36	73	80

[a] TMSTFMS was used as a Lewis acid. [b] 2.0 equivalents of Lewis acid were used.

quently, for the purpose of this study, compound **29** was prepared in 65% yield and with 94% *de* (entry 17).

Next, we attempted to introduce an alkyl group at the α-position of **29** by using previously discussed reaction conditions. Compound **29** underwent α-methylation after treatment with 1.2 equivalents of NaHMDS and three equivalents of methyl iodide at −78°C in toluene to afford ethyl (5*S*)-allyl-*N*-benzyloxycarbonyl-(2*R*)-methylprolinate (**30**) as a mixture of diastereomers (Table 9).

Table 9. α-Methylation of ethyl (5*S*)-allyl-*N*-benzyloxycarbonyl-L-prolinate (**29**).



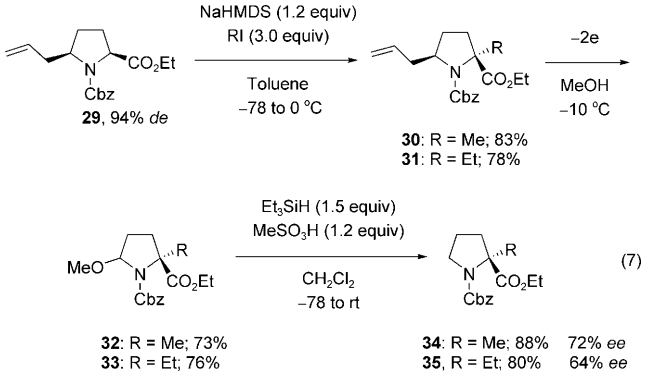
29 **30**

Entry	*T* [°C]	Base	**28** yield [%]	**28** *de* [%][a]
1	−78 to RT	NaHMDS	78	70
2[b]	−78 to 0	NaHMDS	41	72
3	−78 to 0	NaHMDS	83	76
4	−78	NaHMDS	60	76
5[c]	−70	NaHMDS	69	76
6	−78	LiHMDS	41	72
7	−78 to RT	KHMDS	70	80
8	−78	KHMDS	40	84
9[d]	−78 to RT	NaHMDS	50	74
10[e]	−78	NaHMDS	50	40
11[f]	−78 to RT	NaHMDS	trace	–
12[g]	−78 to RT	NaHMDS	trace	–

[a] Determined by using a GC column. [b] The reaction was carried out in THF. [c] MeI was added before the base. [d] Dimethylsulfate was used as the methylating agent. [e] DME was used as an additive. [f] Methyl *p*-toluenesulfonate was used as a methylating agent. [g] Methyl trifluoromethanesulfonate was used as a methylating agent.

The reaction from −78 to 0°C in toluene and THF gave an improvement in both yield and selectivity (Table 9, entries 1–4). Addition of the electrophile before the base gave no observable improvement (entry 5). KHMDS improved selectivity though the yields were somewhat low, whereas LiHMDS gave poor yields and selectivities (entries 6–8). A change of methylating agents to the more reactive dimethyl sulfate gave an average yield and comparable selectivity, whereas methyl *p*-toluenesulfonate and methyl trifluoromethanesulfonate gave only trace amounts of products (entries 9, 11, and 12). Addition of 1,2-dimethoxyethane (DME)[11i] had detrimental effects on selectivity (entry 10).

With consideration to yield and selectivity, **30** was prepared according to conditions in entry 3. Electrochemical α-deallylation and chemical demethoxylation of **30** yielded ethyl *N*-benzyloxycarbonyl-(2*R*)-methylprolinate (**34**)[18a] with 72% *ee*. A change of the electrophile to ethyl iodide gave the resultant quaternary amine, ethyl *N*-benzyloxycarbonyl-(2*R*)-ethylprolinate (**35**)[18c] with 64% *ee* [Eq. (7)].



Conclusion

We have presented a novel approach to the deallylation of α-allyl-*N*-acylated cyclic amines by using an electrochemical method. We have also applied the method to the debenzylation of α-benzyl-*N*-acylated cyclic amines. We have demonstrated a generalization of this method by changing the size of the cyclic amines and the *N*-acyl groups. In all the cases, the yields were moderate to high. We have also shown the methods for diastereoselective α′-allylation of *N*-benzyloxycarobonylpipecolinate and *N*-benzyloxycarobonylprolinate. Whereas pipecolinate requires allyl-TMS to yield only the *cis* diastereomer, prolinate requires a bulky Lewis acid and allylating reagents to give good selectivity. This information is important for chemists interested in the diastereoselective allylation of amino acid esters since they are important building blocks for asymmetric synthesis. Finally, by using an allyl group to achieve asymmetric induction,[19] we have successfully prepared optically active cyclic quaternary amino acid esters with up to 99% *ee*.

Experimental Section

General: All commercial materials, reagents and solvents, were used without further purification unless stated otherwise. Electrochemical reactions were carried out by the use of the DC Power Supply (GP 050–2) of Takasago Seisakusho. HPLC analyses were achieved by using LC-10AT *VP* and SPD-10A *VP* of Shimadzu Seisakusho. ^{1}H NMR spectra were measured at 500, 400, or 300 MHz with TMS as an internal standard. ^{13}C NMR spectra were measured at 125, 100, or 75 MHz. IR spectra were obtained on Shimadzu FTIR-8100A. Mass spectra were obtained on a JEOL JMS-DX 303 instrument. A cyclic voltammogram was measured in 0.1 M Et_4NBF_4/MeCN solution by using glassy-carbon as a working electrode, platinum as a counter electrode, and Ag/0.01 M $AgNO_3$ as a reference electrode. Silica-gel column chromatography was performed by using a mixed solvent of hexane and ethyl acetate. Analytical TLC was performed on Merck silica gel 60 F_{254} plates (0.25 mm). Electrochemical oxidation was carried out by using the DC Power Supply (GP 050–2) of Takasago Seikakusho. Reactions were carried out in an undivided glass cell by using platinum plate electrodes (10×20 mm), glassy carbon electrodes (50×12×2 mm), or graphite electrodes (50×12×2 mm).

General procedure for the preparation of α-allyl-*N*-acyl amino acids 5a–j: BF_3·OEt_2 (6 mmol) was added dropwise to a flask (50 mL) containing α-methoxy-*N*-acyl cyclic amine **4a–j**[20] (5 mmol) and allyltrimethylsilane (6 mmol) in CH_2Cl_2 (10 mL) at −78°C. The mixture was stirred and the

reaction temperature elevated gradually to room temperature over 6 h. Progress was monitored by TLC. After completion of the reaction, water (10 mL) was added and the mixture was extracted by using $CHCl_3$ (3× 10 mL). The combined organic layers were dried with anhydrous $MgSO_4$ and filtered. The filtrate was concentrated in vacuo. The residue was purified through silica-gel column chromatography to give a quantitative yield of the α-allyl amines.

Compounds **5a**,[21] **5b**,[22] **5c**,[23] **5e**,[24] **5f**,[25] **5g**[26], and **5i**[27] are known and their spectroscopic datas is available in the literature.

α-Allyl-N-*methoxycarbonylazocane* (***5d***): Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.81–5.67 (m, 1H), 5.01 (d, J = 4.8 Hz, 1H), 4.97 (s, 1H), 4.14–3.07 (m, 0.5H), 3.94–3.90 (m, 0.5H), 3.70 (d, J = 3.9 Hz, 3H), 3.54–3.39 (m, 1H), 2.98–2.88 (m, 1H), 2.19–2.13 (m, 2H), 1.67–1.45 ppm (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.18, 156.60 (1C), 135.35, 135.03 (1C), 116.84, 116.64 (1C), 55.79, 52.20, 52.09 (1C), 39.52, 39.31 (1C), 28.88, 27.90, 26.90, 26.29, 26.57, 24.41 ppm; IR (neat): $\tilde{\nu}$ = 3077, 2926, 2857, 1642, 1478, 1441, 1404, 1347, 1244, 1146, 1069, 994, 914 cm^{-1}; HR-FAB: *m*/*z*: calcd for $C_{12}H_{22}NO_2$: 212.1669 $[M+H]^+$; found: 212.1671.

α-Allyl-N-*benzyloxycarbonylazocane* (***5h***): Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.35 (m, 5H), 5.86–5.63 (m, 1H), 5.14 (d, J = 6.9 Hz, 2H), 5.01–4.94 (m, 2H), 4.19–4.13 (m, 0.5H), 4.08–4.03 (m, 0.5H), 3.80–3.42 (m, 1H), 3.02–2.89 (m, 1H), 2.21–2.10 (m, 2H), 1.90–1.70 (m, 1H), 1.67–1.47 ppm (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.46, 155.84 (1C), 137.16, 137.08 (1C), 135.29, 135.01 (1C), 128.30, 127.75, 127.71, 127.61, 127.54, 116.91, 116.70 (1C), 66.66, 66.61 (1C), 55.87, 39.49, 39.31 (1C), 28.95, 27.97, 26.81, 26.57, 26.16, 24.37 ppm; IR (neat): $\tilde{\nu}$ = 3069, 2926, 2857, 1705, 1642, 1497, 1474, 1416, 1343, 1181, 1144, 1061, 914, 698 cm^{-1}; HR-FAB: *m*/*z*: calcd for $C_{18}H_{26}NO_2$: 288.1669 $[M+H]^+$; found: 288.1969.

α-Allyl-N-*benzoylazepane* (***5j***): Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.32 (m, 5H), 5.91–5.85 (m, 0.5H), 5.50–5.44 (m, 0.5H), 5.13–4.92 (m, 2H), 4.66–4.71 (m, 0.5H), 4.32 (br d, J = 13.5 Hz, 0.5H), 3.72–3.67 (m, 0.5H), 3.49 (br d, J = 16.2 Hz, 0.5H), 3.02–2.98 (m, 0.5H), 2.81–2.72 (m, 0.5H), 2.35 (t, J = 6.9 Hz, 1H), 2.21–1.78 (m, 5H), 1.48–1.25 ppm (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.42, 171.34 (1C), 137.90, 137.59 (1C), 135.13, 133.95 (1C), 128.50, 128.45, 128.27, 126.25, 126.00, 117.64, 116.87 (1C), 57.10, 52.99 (1C), 44.08, 40.39 (1C), 40.13, 39.10 (1C), 34.18, 32.99 (1C), 30.51, 30.07 (1C), 28.99, 27.62 (1C), 24.93, 24.65 ppm (1C); IR (neat): $\tilde{\nu}$ = 2928, 2855, 1636, 1578, 1495, 1445, 1422, 1375, 1347, 1283, 1177, 1138, 1119, 1075, 972, 914, 779, 704 cm^{-1}; HR-FAB: *m*/*z*: calcd for $C_{16}H_{22}NO$: 244.1707 $[M+H]^+$; found: 244.1708.

α-(1-Myristylallyl)-N-*benzyloxycarbonylpiperidine* (***6***): Trimethyl-1-tetradecylallylsilane (10.0 mmol) was added to a solution of **4f** (5.0 mmol) in CH_2Cl_2 (60 mL) and the mixture was stirred at −78 °C for 10 min. $BF_3{\cdot}OEt_2$ (6.0 mmol) was added dropwise and the temperature was allowed to rise gradually to room temperature over 4 h. Water (30 mL) was added and the mixture was extracted with $CHCl_3$ (3×20 mL). The organic layer was dried by using anhydrous magnesium sulfate and filtered. The filtrate was concentrated in vacuo and the concentrate was purified by using silica-gel column chromatography to give **6** (2.6 mmol). Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.34 (m, 5H), 5.47–5.40 (m, 0.5H), 5.33–5.29 (m, 0.5H), 5.18–5.11 (m, 4H), 4.30 (br s, 1H), 4.04 (br d, J = 11.1 Hz, 1H), 2.89–2.80 (m, 1H), 2.33–2.17 (m, 1H), 1.94–1.90 (m, 1H), 1.61–1.55 (m, 5H), 1.25 (br s, 26H), 0.88 ppm (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.53, 137.11, 133.15, 128.54, 128.38 (2C), 127.75, 127.66, 126.30, 66.76, 50.72, 39.23, 33.07, 32.54, 31.90, 29.67–29.16 (m, 10C), 27.40, 25.45, 22.66, 18.71, 14.09 ppm; IR (neat): $\tilde{\nu}$ = 3032, 2936, 2855, 1707, 1609, 1498, 1468, 1421, 1211, 1170, 1140, 1044, 968, 696 cm^{-1}; HR-FAB: *m*/*z*: calcd for $C_{30}H_{50}NO_2$: 456.3842 $[M+H]^+$; found: 456.3841.

α-(4-tert-Butylbenzyl)-N-*benzyloxycarbonylpyrrolidine* (***9***): Freshly prepared 4-*tert*-butylbenzyl magnesium chloride (10.0 mmol) in THF (5 mL) was added to a solution of **4e** (5.0 mmol) in CH_2Cl_2 (60 mL) and the mixture was stirred at −78 °C for 10 min. $BF_3{\cdot}OEt_2$ (6.0 mmol) was added dropwise and the temperature was allowed to rise gradually to room temperature over 4 h. Saturated NH_4Cl (30 mL) was added and the mixture was extracted with $CHCl_3$ (3×20 mL). The organic layer was dried by using anhydrous magnesium sulfate and filtered. The filtrate was concentrated in vacuo and the concentrate was purified by using silica-gel column chromatography to give **9** (2.8 mmol). Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.15 (m, 9H), 5.16 (s, 2H), 4.10–4.03 (m, 1H), 3.43–3.39 (m, 2H), 3.18 and 2.30 (dd, J = 12.8 Hz, 1H), 2.57–2.48 (m, 1H), 1.76 (br s, 4H), 1.30 ppm (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.89, 154.74 (1C), 148.99, 148.90 (1C), 135.75, 129.14, 128.95, 128.41 (3C), 127.88 (2C), 125.16 (2C), 66.80, 66.39 (1C), 59.24, 58.76 (1C), 46.74, 46.51 (1C), 39.98, 39.66 (1C), 38.80, 34.29, 31.32 (2C), 27.71, 28.83 (1C), 23.35, 22.54 ppm (1C); IR (neat): $\tilde{\nu}$ = 3090, 3030, 2966, 2874, 2361, 1609, 1588, 1498, 1456, 1336, 1269, 1115, 978, 916, 698 cm^{-1}; HR-FAB: *m*/*z*: calcd for $C_{23}H_{30}NO_2$: 352.2290 $[M+H]^+$; found: 352.2292.

General procedure for electrochemical deallylation of α-allyl-*N*-acyl amino acids 5a–j: The substrate (0.5 mmol) and Et_4NBF_4 (0.1 mmol) were placed in a beaker-type cell containing a stirring bar. Methanol (2 mL) and acetonitrile (8 mL) were added and the mixture was stirred at 0 °C. The graphite anode and platinum cathode were fitted and 2 F mol^{-1} of electricity were passed through. The reaction mixture was transferred into a flask (25 mL) and the solvent was evaporated. Water (10 mL) was added, the mixture was extracted with AcOEt (3×8 mL), and the combined organic layer was dried by using anhydrous $MgSO_4$ and filtered. The solvent was removed under vacuo to give the methoxy compounds **4a–k**.[20]

α-Methoxy-N-*methoxycarbonylazocane* (***4d***): Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.21–5.18 (m, 0.5H), 5.01–4.95 (m, 0.5H), 3.64 and 3.58 (s, 3H), 3.29–3.20 (m, 2H), 3.08, 3.05 (s, 3H), 1.70–1.32 ppm (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.68, 156.47 (1C), 85.73, 85.64 (1C), 54.29, 53.92 (1C), 52.31, 52.05 (1C), 48.18, 47.21 (1C), 39.81, 39.29 (1C), 29.28, 28.98 (1C), 27.36, 26.74 (1C), 25.74, 25.58 (1C), 23.43, 22.66 ppm (1C); IR (neat): $\tilde{\nu}$ = 2936, 2859, 1479, 1445, 1408, 1277, 1192, 1028, 885, 773 cm^{-1}; HR-FAB: *m*/*z*: calcd for $C_9H_{16}NO_2$: 170.1194 $[M-OMe]^+$; found: 170.1195.

α-Methoxy-N-*benzyloxycarbonylazocane* (***4h***): Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35 (br s, 5H), 5.35–5.30 (m, 1H), 5.19, 5.15 (dd, J = 9.28 Hz, 2H), 3.55–3.36 (m, 2H), 3.19, 3.11 (s, 3H), 1.82–1.43 ppm (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.04, 155.80 (1C), 137.02, 136.54 (1C), 128.30, 128.22, 127.78, 127.57, 127.51, 85.71, 66.87, 66.54 (1C), 55.38, 54.04 (1C), 48.33, 47.26 (1C), 39.90, 39.37 (1C), 29.31, 29.08 (1C), 27.46, 26.77 (1C), 26.06, 25.59 (1C), 23.43, 22.68 ppm (1C); IR (neat): $\tilde{\nu}$ = 3034, 2934, 2860, 1709, 1478, 1416, 1275, 1190, 1144, 1084, 1028, 885, 698 cm^{-1}; HR-FAB: *m*/*z*: calcd for $C_{15}H_{20}NO_2$: 246.1481 $[M-OMe]^+$; found: 246.1480.

General procedure for the preparation of α-benzyl-*N*-acyl amino acids 8a–h: Freshly prepared benzylmagnesium chloride (7.5 mmol) was added with a syringe under a nitrogen atmosphere to a two-neck flask (50 mL) containing α-methoxy-*N*-acyl cyclic amine (5 mmol) in CH_2Cl_2 (10 mL) at −78 °C. The solution was stirred at −78 °C for 1 h and $BF_3{\cdot}OEt_2$ (6 mmol) was added dropwise. The reaction was stirred for a further 2 h and the reaction progress was monitored by TLC. After completion of the reaction, saturated ammonium chloride solution was added (30 mL) and the resulting mixture was extracted by using $CHCl_3$ (3×10 mL). The combined organic layer was washed with brine (2×10 mL), dried using anhydrous $MgSO_4$, and filtered. The filtrate was concentrated in vacuo. The residue was purified through silica-gel column chromatography to give a quantitative yield of the α-benzylated amines **8a–h**.

Compounds **8a**[28] and **8b**[28] are known and their spectroscopic data is available in the literature.

α-Benzyl-N-*methoxycarbonylazepane* (***8c***): Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.25–7.14 (m, 5H), 4.28–4.38 (m, 0.5H), 4.15–4.01 (m, 0.5H), 3.74–3.70 (m, 3H), 3.53–3.47 (m, 2H), 2.74–2.58 (m, 2H), 1.90–1.14 ppm (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.92, 138.77, 138.70 (1C), 129.42, 129.25, 128.13, 126.08, 126.05, 62.69, 57.46, 57.26 (1C), 52.31, 52.12 (1C), 41.98, 41.45 (1C), 33.65, 32.77 (1C), 29.82, 29.69 (1C), 28.90, 28.16 (1C), 22.43 ppm; IR (neat): $\tilde{\nu}$ = 3027, 2930, 2855, 1603, 1495, 1474, 1437, 1406, 1375, 1279, 1207, 1103, 1011, 970, 774, 702 cm^{-1}; HR-FAB: *m*/*z*: calcd for $C_{15}H_{22}NO_2$: 248.1653 $[M+H]^+$; found: 248.1653.

α-Benzyl-N-*methoxycarbonylazocane* (***8d***): Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.24–7.11 (m, 5H), 4.41–4.11 (m, 0.5H), 4.08–4.01

(m, 0.5H), 3.67 (d, J=9.0 Hz, 3H), 3.44–3.32 (m, 2H), 3.30–2.90 (m, 0.5H), 2.89 (dd, J=6.0 Hz, 0.5H), 2.63 (dddd, J=7.7 Hz, 1H), 1.75–1.53 ppm (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=156.85, 156.45 (1C), 138.91, 138.87 (1C), 129.34, 129.18 (1C), 129.01, 128.98 (1C), 128.13, 128.12 (1C), 127.58, 126.24 (1C), 126.08, 126.03 (1C), 58.02, 57.96 (1C), 52.18, 51.93 (1C), 42.12, 41.90 (1C), 41.39, 41.02 (1C), 28.16, 27.98 (1C), 26.97, 26.89 (1C), 26.23, 26.12 (1C), 26.08, 25.89 (1C), 24.71, 24.59 ppm (1C); IR (neat): $\tilde{\nu}$=3027, 2930, 2857, 1709, 1603, 1480, 1441, 1437, 1404, 1348, 1223, 1190, 1146, 1069, 1030, 974, 774, 700 cm^{-1}; HR-FAB: m/z: calcd for $C_{16}H_{24}NO_2$: 262.1814 $[M+H]^+$; found: 262.1815.

α-Benzyl-N-benzyloxycarbonylpyrrolidine (***8e***): Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.39–7.34 (m, 5H), 7.25–7.21 (m, 5H), 5.17 (s, 2H), 4.09 (brs, 1H), 3.40 (brs, 2H), 3.19 (brd, J=12.6 Hz, 0.5H), 3.03 (brd, J=10.5 Hz, 0.5H), 2.65–2.57 (m, 1H), 1.77–1.67 ppm (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=154.89, 138.80, 129.51, 129.31, 128.41 (2C), 128.28 (2C), 128.07, 127.99, 127.93, 127.75, 126.15, 66.87, 66.43 (1C), 59.20, 58.74 (1C), 46.79, 46.53 (1C), 40.55, 39.37 (1C), 29.67, 28.83 (1C), 23.39, 22.58 (1C) ppm; IR (neat): $\tilde{\nu}$=3029, 2878, 1713, 1603, 1586, 1497, 1455, 1418, 1360, 1279, 1213, 1188, 1030, 916, 768, 700 cm^{-1}; HR-FAB: m/z: calcd for $C_{19}H_{22}NO_2$: 296.1665 $[M+H]^+$; found: 296.1667.

α-Benzyl-N-*benzyloxycarbonylpiperidine* (***8f***): Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.31–7.18 (m, 10H), 5.18–4.96 (m, 2H), 4.49 (brs, 1H), 4.12 (brd, J=12.0 Hz, 1H), 3.04–2.87 (m, 3H), 1.71–1.46 ppm (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=155.45, 138.94, 136.88, 129.13 (2C), 128.33 (2C), 128.31 (2C), 127.76 (2C), 127.73, 126.15, 66.82, 52.53, 39.52, 36.10, 25.41 (2C), 18.77 ppm; IR (neat): $\tilde{\nu}$=3029, 2942, 2861, 1709, 1586, 1603, 1497, 1269, 1198, 1167, 986, 912, 702 cm^{-1}; HR-FAB: m/z: calcd for $C_{20}H_{24}NO_2$: 310.1829 $[M+H]^+$; found: 310.1831.

α-Benzyl-N-*benzyloxycarbonylazepane* (***8g***): Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.35–7.18 (m, 10H), 5.18–4.91 (m, 2H), 4.41–4.26 (m, 0.5H), 4.19–4.10 (m, 0.5H), 3.87 (brd, J=14.1 Hz, 0.5H), 3.74 (brd, J=15.0 Hz, 1H), 3.52–3.38 (m, 0.5H), 2.87–2.61 (m, 2H), 1.91–1.16 ppm (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=156.08, 138.68, 138.61 (1C), 137.21, 136.91 (1C), 129.41, 129.33 (1C), 129.25, 128.70 (1C), 128.43, 128.37, 128.33 (1C), 128.17, 128.13 (1C), 127.83, 127.77, 127.69 (1C), 127.62, 127.57 (1C), 127.52, 127.38 (1C), 126.10, 126.05 (1C), 66.87, 66.63 (1C), 57.43, 57.37 (1C), 42.12, 42.01 (1C), 41.52, 40.87 (1C), 33.56, 32.90 (1C), 29.79, 29.58 (1C), 29.50, 28.21 (1C), 25.07 ppm; IR (neat): $\tilde{\nu}$=3031, 2928, 2855, 1709, 1603, 1586, 1603, 1497, 1420, 1306, 1269, 1204, 1103, 1086, 1001, 770, 698 cm^{-1}; HR-FAB: m/z: calcd for $C_{21}H_{26}NO_2$: 324.1955 $[M+H]^+$; found: 324.1956.

α-Benzyl-N-*benzyloxycarbonylazocane* (***8h***): Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.32–7.05 (m, 10H), 5.11–5.02 (m, 2H), 4.44–4.22 (m, 0.5H), 4.19–4.08 (m, 0.5H), 3.53 (brd, J=15.6 Hz, 0.5H), 3.40 (brd, J=14.1 Hz, 0.5H), 3.04–2.92 (m, 1H), 2.83–2.55 (m, 2H), 1.69–1.44 ppm (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=156.17, 155.78 (1C), 138.86, 137.21, 136.98 (1C), 129.35, 129.20 (1C), 128.35, 128.31, 128.20, 128.15, 127.79, 127.72, 127.67, 127.57, 127.51 (1C), 126.12, 126.06 (1C), 66.68, 66.57 (1C), 58.12, 58.05 (1C), 41.39, 40.97 (1C), 28.49, 28.06 (1C), 26.93, 26.84, 26.72, 26.21, 24.75, 24.61 ppm (1C); IR (neat): $\tilde{\nu}$=3031, 2932, 2857, 1709, 1605, 1586, 1603, 1497, 1418, 1146, 1061, 1030, 970, 702 cm^{-1}; HR-FAB: m/z: calcd for $C_{22}H_{28}NO_2$: 338.2123 $[M+H]^+$; found: 338.2123.

General procedure for electrochemical debenzylation of α-benzyl-*N*-acyl amino acids 8a–h: The substrate (0.5 mmol) and Et_4NBF_4 (0.1 mmol) were placed in a beaker-type cell containing a stirring bar. Alcohol (2 mL) and acetonitrile (8 mL) were added and the mixture was stirred at −10 °C. The graphite anode and platinum cathode were fitted and 4 F mol^{-1} of current was passed through. The reaction mixture was transferred into a flask (25 mL) and the solvent was evaporated. Water (10 mL) was added and the mixture was then extracted with AcOEt (3× 8 mL) and the combined organic layer was dried by using anhydrous $MgSO_4$ and filtered. The solvent was removed under vacuo to give the methoxy compounds **4a–h** and **4k**.

Measurement of oxidation potentials: BAS CV-50W was used as a voltametric analyzer. A solution of substrate (0.1 mmol) in MeCN (5 mL) containing Et_4NBF_4 (0.1 m) was measured. The reference electrode was Ag/$AgNO_3$ in saturated aqueous KCl, whereas glassy carbon was the working electrode, and platinum wire was the counter electrode. The scan rate was 50 mV s^{-1}.

Synthesis of methyl (6*S*)-allyl-*N*-benzyloxycarbonyl-D-pipecolinate (16):[12b] HCl/MeOH solution (1 N 100 mL) was added to D-pipecolinic acid (20 mmol) in a round-bottomed flask (500 mL) and the solution was stirred at 50 °C for 6 h. Then the solvent was evaporated. The resulting ester (20 mmol) in dichloromethane (100 mL) was treated with triethylamine (50 mmol), 4-dimethylaminopyridine (DMAP) (2 mmol), and carboxybenzyl chloride (Cbz-Cl) (24 mmol), and the mixture was stirred at room temperature for 12 h. Water (100 mL) was added to quench the reaction and the mixture was extracted by using AcOEt (3×50 mL). The organic layer was dried by using anhydrous magnesium sulphate, filtered, and concentrated in vacuo. The resulting concentrate was purified by silica-gel column chromatography to yield *N*-benzyloxycarbonyl-D-pipecolinate (**14**; 19.6 mmol). Electrochemical oxidation (2 F mol^{-1}) of **14** (10 mmol) in methanol (50 mL) by using an undivided cell graphite anode at 0 °C yielded α′-methoxy derivative **15** (9.2 mmol).

Allyltrimethylsilane (10.8 mmol) was added to a solution of **15** (9 mmol) in CH_2Cl_2 (30 mL) and the mixture was stirred at −78 °C for 10 min. BF_3·OEt_2 (10.8 mmol) was added dropwise and the temperature allowed to rise gradually to room temperature over 4 h. Water (30 mL) was added and the mixture was extracted with $CHCl_3$ (3×20 mL). The organic layer was dried by using anhydrous magnesium sulfate and filtered. The filtrate was concentrated in vacuo and the concentrate was purified by using silica-gel column chromatography to give **16** (7.9 mmol).

*Methyl (6*S*)-allyl*-N-*benzyloxycarbonyl*-D-*pipecolinate* (***16***): The *de* value was determined to be >99% by gas chromatography (Shinwa Chemical Industries, HR-1, 0.25 mmØ×25 m) at a constant temperature of 170 °C and a retention time of 32.82 min. Colorless oil; $[\alpha]_D^{28}$=77.75 (c=1.0 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.35–7.33 (m, 5H), 5.79–5.65 (m, 1H), 5.18 (s, 2H), 5.05–5.03 (d, J=6 Hz, 1H), 4.99 (s, 1H), 4.89 (brs, 1H), 4.24 (t, J=5.7 Hz, 1H), 3.66 (s, 3H), 2.47–2.14 (m, 3H), 1.73–1.50 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=172.99, 156.15 (br), 136.58, 135.92, 128.34 (2C), 127.85, 127.69 (2C), 116.87, 67.24, 55.52, 51.97, 50.89, 38.12 (br), 25.79 (2C), 15.31 ppm; IR (neat): $\tilde{\nu}$=3069, 3033, 2950, 2867, 1640, 1499, 1412, 1211, 1152, 1071, 1003, 916, 698 cm^{-1}; HR-FAB: m/z: calcd for $C_{18}H_{24}NO_4$: 318.1721 $[M+H]^+$; found: 318.1723.

General α-alkylation protocol for α′-allyl-*N*-acyl-α-amino acid esters: NaHMDS (0.6 mmol) was added to the substrate (0.5 mmol) in dry solvent (2 mL) under a nitrogen atmosphere at −78 °C. The temperature was elevated to −20 °C and the mixture stirred for 30 min. The reaction temperature was restored to −78 °C and alkyl iodide or bromide (1.5 mmol) was gradually added. The temperature was then gradually allowed to rise and the reaction was monitored by using TLC. Saturated ammonium chloride solution (10 mL) was added and the mixture was extracted by using AcOEt (3×10 mL). The organic extract was washed with brine (3×5 mL), dried by using anhydrous magnesium sulfate, and filtered. The filtrate was concentrated under reduced pressure and the concentrate was purified by using silica-gel column chromatography to yield α′-allyl-*N*-acyl-α-alkyl-α-amino acid esters **21**, **22a–h**, **30**, and **31**.

*Methyl (6*S*)-allyl*-N-*benzyloxycarbonyl-(2*R*)-methylpipecolinate* (***21***): The *de* value was determined to be >99% by gas chromatography (Shinwa Chemical Industries, HR-1, 0.25 mmØ×25 m) at a constant temperature of 170 °C and a retention time of 68.83 min. Colorless oil; $[\alpha]_D^{32}$=11.46 (c=1.25 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.35–7.34 (m, 5H), 5.80–5.77 (m, 1H), 5.11 (s, 2H), 5.09 (s, 0.5H), 5.03 (t, J=9.8 Hz, 1.5H), 4.13 (t, J=7.0 Hz, 1H), 3.54 (brs, 3H), 2.59–2.57 (m, 1H), 2.34–2.31 (m, 1H), 2.20–2.18 (m, 1H), 1.83–1.82 (m, 2H), 1.75–1.66 (m, 3H), 1.59 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=175.47, 155.12, 136.51, 135.80, 128.36 (3C), 128.00, 127.92, 116.78, 67.05, 60.29, 52.13, 51.20, 40.22, 30.99, 22.19, 21.67, 12.35 ppm; IR (neat): $\tilde{\nu}$=2950, 2361, 1742, 1736, 1698, 1638, 1541, 1509, 1499, 1458, 1401, 1341, 1271, 1227, 1134, 1065, 698 cm^{-1}; HR-FAB: m/z: calcd for $C_{19}H_{26}NO_4$: 332.1863 $[M+H]^+$; found: 332.1863.

*Methyl (6*S*)-allyl*-N-*benzyloxycarbonyl-(2*R*)-ethylpipecolinate* (***22a***): The *de* value was determined to be >99% by gas chromatography (Shinwa Chemical Industries HR-1, 0.25 mmØ×25 m) at a constant temperature of 170 °C and a retention time of 70.83 min. Colorless oil; $[\alpha]_D^{32}$=36.26

($c=2.85$ in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta=7.35$–7.31 (m, 5H), 5.78–5.70 (m, 1H), 5.23–4.95 (m, 4H), 4.23–4.08 (m, 1H), 3.57 (brs, 3H), 2.57–2.51 (m, 1H), 2.39–2.31 (m, 1H), 2.10–2.07 (m, 3H), 1.82–1.63 (m, 5H), 0.95 ppm (t, $J=7.6$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=$ 175.31, 155.62, 136.04, 128.36, 128.32, 128.01, 127.98, 127.94, 127.89, 116.70, 67.00, 66.54, 63.16, 51.92, 51.86, 39.36, 29.74, 29.46, 22.90, 13.38, 9.41 ppm; IR (neat): $\tilde{\nu}=3069$, 3034, 2951, 2880, 1748, 1744, 1640, 1588, 1499, 1456, 1402, 1341, 1256, 1219, 1134, 1090, 1030, 1001, 916, 698 cm^{-1}; HR-FAB: m/z: calcd for $C_{20}H_{28}NO_4$: 346.2032 $[M+H]^+$; found: 346.2034.

Methyl (2S,6S)-diallyl-N-*benzyloxycarbonylpipecolinate* (**22b**): The *de* value was determined to be >99% by gas chromatography (Shinwa Chemical Industries, HR-1, 0.25 mmØ×25 m) at a constant temperature of 200°C and a retention time of 29.80 min. Colorless oil; $[\alpha]_D^{32}=9.45$ ($c=$ 0.82 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta=7.35$–7.29 (m, 5H), 6.01–5.92 (m, 1H), 5.78–5.70 (m, 1H), 5.22–5.00 (m, 6H), 4.16–4.10 (m, 1H), 3.57 (brs, 3H), 2.89 (dd, $J=6.4$ Hz, 1H), 2.80–2.72 (m, 1H), 2.68–2.51 (m, 1H), 2.38–2.32 (m, 1H), 2.13–2.05 (m, 1H), 1.86–1.50 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=175.03$, 155.51, 135.94, 134.88, 128.50, 128.41, 128.08, 127.93, 127.76, 117.69, 116.85, 67.11, 62.65, 52.05, 51.82, 39.68, 29.75, 25.85, 22.59, 15.37, 12.66 ppm; IR (neat): $\tilde{\nu}=2950$, 1744, 1701, 1640, 1499, 1456, 1402, 1339, 1314, 1277, 1223, 1001, 916, 769, 698 cm^{-1}; HR-FAB: m/z: calcd for $C_{21}H_{28}NO_4$: 358.2032 $[M+H]^+$; found: 358.2033.

Methyl (6S)-allyl-N-*benzyloxycarbonyl-(2S)-(2-propynyl)pipecolinate* (**22c**): The *de* value was determined to be 81% by gas chromatography (Shinwa Chemical Industries, HR-1, 0.25 mmØ×25 m) at a constant temperature of 200°C and a retention time of 30.00 (major) and 32.67 min (minor). Colorless oil; $[\alpha]_D^{32}=-5.33$ ($c=1.00$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta=7.34$–7.30 (m, 5H), 5.76–5.71 (m, 1H), 5.13 (s, 2H), 5.07–5.00 (m, 2H), 4.16–4.13 (m, 1H), 3.59 (brs, 3H), 3.05 (s, 2H), 2.59–2.53 (m, 1H), 2.39–2.22 (m, 1H), 2.19–2.12 (m, 2H), 2.03–2.01 (m, 1H), 1.84–1.63 ppm (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=174.07$, 155.53, 135.83, 128.41, 128.32, 128.03, 127.93, 127.76, 116.95, 80.89, 70.57, 67.29, 62.01, 52.32, 51.78, 39.77, 30.31, 27.04, 25.85, 22.65, 12.97 ppm; IR (neat): $\tilde{\nu}=2951$, 2120, 1742, 1698, 1640, 1456, 1402, 1339, 1312, 1296, 1219, 1159, 1069, 916, 698 cm^{-1}; HR-FAB: m/z: calcd for $C_{21}H_{26}NO_4$: 356.1858 $[M+H]^+$; found: 356.1857.

Methyl (6S)-allyl-N-*benzyloxycarbonyl-(2S)-(2-butenyl)pipecolinate* (**22e**): A 3:1 (*E*/*Z*) mixture of geometric isomers was determined by gas chromatography (Shinwa Chemical Industries, HR-1, 0.25 mmØ×25 m) at a constant temperature of 200°C and a retention time of 38.17 (major) and 41.33 min (minor). Colorless oil; $[\alpha]_D^{28}=-15.08$ ($c=0.81$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta=7.35$–7.30 (m, 5H), 5.82–5.60 (m, 1H), 5.57–5.43 (m, 2H), 5.16–5.00 (m, 4H), 4.14–4.11 (m, 1H), 3.57 (brs, 3H), 2.86–2.71 (m, 2H), 2.58–2.54 (m, 1H), 2.39–2.28 (m, 1H), 2.12–2.01 (m, 1H), 1.87–1.61 ppm (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=175.22$, 155.51, 136.02, 128.38 (2C), 128.27, 128.08, 127.94, 127.19, 126.19, 126.10, 116.81, 116.78 (1C), 67.11, 67.06 (1C), 62.88, 52.05, 52.00 (1C), 51.92, 51.83 (1C), 39.65, 39.51 (1C), 29.77, 22.64, 18.03, 13.22, 12.97 (1C), 12.77 ppm; IR (neat): $\tilde{\nu}=2949$, 1744, 1640, 1499, 1456, 1402, 1339, 1312, 1217, 1130, 976, 914, 769, 698 cm^{-1}; HR-FAB: m/z: calcd for $C_{22}H_{30}NO_4$: 372.2179 $[M+H]^+$; found: 372.2180.

Methyl (6S)-allyl-N-*benzyloxycarbonyl-(2S)-(2-butynyl)pipecolinate* (**22f**): The *de* value was determined to be 99% by gas chromatography (Shinwa Chemical Industries, HR-1, 0.25 mmØ×25 m) at a constant temperature of 200°C and a retention time of 43.17 min. Colorless oil; $[\alpha]_D^{28}=10.42$ ($c=5.0$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta=7.35$–7.34 (m, 5H), 5.80–5.68 (m, 1H), 5.18–5.00 (m, 4H), 4.20–4.13 (m, 1H), 3.57 (brs, 3H), 2.97 (brs, 1H), 2.64–2.11 (m, 3H), 1.86–1.78 (m, 5H), 1.59 (s, 3H), 1.52–1.50 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=$ 175.31, 172.96 (m, 1C), 155.44, 136.56, 136.34 (1C), 135.89, 128.31, 128.30, 127.92, 127.87, 127.66, 116.85, 116.76 (1C), 75.39, 67.22, 67.05 (1C), 62.19, 52.50, 52.11 (1C), 51.95, 51.68 (1C), 39.65, 30.48, 27.28, 25.77, 15.29, 13.05, 3.54 ppm; IR (neat): $\tilde{\nu}=3069$, 2951, 2235, 2051, 1640, 1588, 1499, 1003, 916, 804, 777, 700 cm^{-1}; HR-FAB: m/z: calcd for $C_{22}H_{28}NO_4$: 370.2016 $[M+H]^+$; found: 370.2016.

Methyl (6S)-allyl-N-*methoxycarbonyl-(2R)-methylpipecolinate* (**22h**): The *de* value was determined to be 98% by gas chromatography (Shinwa Chemical Industries, HR-1, 0.25 mmØ×25 m) at a constant temperature of 170°C and a retention time of 7.70 (minor) and 8.33 min (major). Colorless oil; $[\alpha]_D^{28}=17.38$ ($c=1.82$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta=5.70$–5.58 (m, 1H), 4.96–4.87 (m, 2H), 3.93–3.88 (m, 1H), 3.54 (s, 3H), 3.51 (s, 3H), 2.42–2.37 (m, 1H), 2.19–2.03 (m, 2H), 1.66–1.50 (m, 4H), 1.42 (s, 3H), 1.36–1.33 ppm (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=175.58$, 155.75, 135.81, 134.67 (1C), 117.91, 116.67 (1C), 60.21, 59.64 (1C), 52.53, 52.25 (1C), 51.09, 41.25, 40.13 (1C), 34.83, 30.94, 30.65 (1C), 21.13, 21.66 (1C), 18.38, 12.32 ppm; IR (neat): $\tilde{\nu}=2953$, 1642, 1449, 1273, 1096, 997, 918, 776, 735 cm^{-1}; HR-FAB: m/z: calcd for $C_{13}H_{22}NO_4$: 256.1551 $[M+H]^+$; found: 256.1551.

Ethyl (5S)-allyl-N-*benzyloxycarbonyl-(2S)-methylprolinate* (**30**): The *de* value was determined to be 76% by gas chromatography (Shinwa Chemical Industries, HR-1, 0.25 mmØ×25 m) at a constant temperature of 200°C and a retention time of 16.17 (minor) and 17.25 min (major). Colorless oil; $[\alpha]_D^{28}=8.14$ ($c=1.0$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta=7.35$–7.32 (m, 5H), 5.87–5.60 (m, 1H), 5.20–4.92 (m, 4H), 4.22–3.90 (m, 3H), 2.79–2.73 (m, 0.5H), 2.64–2.55 (m, 0.5H), 2.27–2.22 (m, 2H), 2.18–1.93 (m, 1H), 1.85–1.75 (m, 2H), 1.52 (d, $J=17.7$ Hz, 3H), 1.23, 1.09 ppm (2t, $J=7.2$, 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=$ 174.41, 174.24 (1C), 153.48, 136.74, 136.37 (1C), 135.40, 135.26 (1C), 128.36, 127.98, 127.88, 127.82, 127.72, 117.09, 66.78, 66.59 (1C), 61.09, 61.05 (1C), 59.32, 58.52 (1C), 37.38, 36.69 (1C), 27.17, 26.15 (1C), 22.27, 20.94 (1C), 18.61, 14.00, 13.85 (1C), 10.91 ppm; IR (neat): $\tilde{\nu}=2979$, 1742, 1499, 1406, 1352, 1273, 1179, 1067, 916, 698 cm^{-1}; HR-FAB: m/z: calcd for $C_{19}H_{26}NO_4$: 332.1876 $[M+H]^+$; found: 332.1878.

Ethyl (5S)-allyl-N-*benzyloxycarbonyl-(2S)-ethylprolinate* (**31**): The *de* value was determined to be 68% by gas chromatography (Shinwa Chemical Industries, HR-1, 0.25 mmØ×25 m) at a constant temperature of 170°C and a retention time of 63.39 (minor) and 65.42 min (major). Colorless oil; $[\alpha]_D^{27}=9.60$ ($c=0.59$ in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta=7.35$–7.31 (m, 5H), 5.80–5.64 (m, 1H), 5.20–5.01 (m, 4H), 4.18–3.91 (m, 3H), 2.83 (brd, $J=12$ Hz, 0.5H), 2.62 (brd, $J=12$ Hz, 0.5H), 2.35–1.98 (m, 6H), 1.78–1.73 (m, 1H), 1.22, 1.10 (2t, $J=7.32$, 6.84 Hz, 3H), 0.87–0.82 ppm (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=175.43$, 155.32, 135.62, 135.49, 128.37, 128.01, 127.89, 127.74, 126.45, 117.02, 66.81, 66.62 (1C), 60.96, 60.32 (1C), 59.43, 57.80 (1C), 38.24, 36.89 (1C), 35.30, 33.89 (1C), 28.32, 28.01 (1C), 27.17, 26.88 (1C), 14.03, 13.90 (1C), 8.64, 8.56 (1C), 6.35 ppm; IR (neat): $\tilde{\nu}=3069$, 2979, 1748, 1640, 1499, 1456, 1412, 1084, 1030, 916, 700 cm^{-1}; HR-FAB: m/z: calcd for $C_{20}H_{28}NO_4$: 346.2025 $[M+H]^+$; found: 346.2026.

General procedure for electrochemical deallylation of α′-allyl-*N*-acyl-α-alkyl-α-amino acid esters 21, 22a–h, 30, and 31: The substrate (0.5 mmol) and Et_4NBF_4 (0.1 mmol) were placed in a beaker-type cell containing a stirring bar. Methanol (2 mL) and acetonitrile (8 mL) were added and the mixture was stirred at −10°C. The graphite anode and platinum cathode were fitted and 5 F mol^{-1} of electricity was passed through. The reaction mixture was transferred into a flask (25 mL) and the solvent was evaporated. Water (10 mL) was added and the mixture was then extracted with AcOEt (3×8 mL). The combined organic layer was dried by using anhydrous $MgSO_4$ and filtered. The solvent was removed under vacuo. The resultant oil was purified through silica-gel column chromatography to give the methoxy derivatives **20**, **23a–c**, **23f**, **32**, and **33**.

Methyl 6-methoxy-N-*benzyloxycarbonyl-(2R)-methylpipecolinate* (**20**): Colorless oil; ^1H NMR (300 MHz, $CDCl_3$): $\delta=7.34$–7.33 (m, 5H), 5.42 (brs, 1H), 5.14 (brs, 2H), 3.68 (brs, 3H), 3.41 (brs, 3H), 2.49–2.41 (m, 1H), 2.21–1.96 (m, 1H), 1.80–1.66 (m, 4H), 1.56 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=175.14$, 174.06 (1C), 154.16, 135.87, 128.37, 128.35, 128.19, 128.13, 124.17, 81.64, 67.58, 67.33 (1C), 60.52, 60.23 (1C), 52.20, 51.99 (1C), 43.24, 32.11, 25.47, 17.83, 12.12 ppm; IR (neat): $\tilde{\nu}=2151$, 1744, 1709, 1657, 1500, 1399, 1339, 1273, 1117, 1092, 909, 700 cm^{-1}; HR-FAB: m/z: calcd for $C_{16}H_{20}NO_4$: 290.1415 $[M-OMe]^+$; found: 290.1417.

Methyl 6-methoxy-N-*benzyloxycarbonyl-(2R)-ethylpipecolinate* (**23a**): Colorless oil; ^1H NMR (300 MHz, $CDCl_3$): $\delta=7.35$–7.34 (m, 5H), 5.45 (s, 1H), 5.19–5.08 (m, 2H), 3.55 (brs, 3H), 3.38 (s, 3H), 2.42–2.35 (m, 2H), 2.01–1.68 (m, 6H), 1.06 ppm (t, $J=7.5$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=175.01$, 156.20, 136.05, 128.45 (2C), 128.37 (2C), 128.19, 82.05, 67.42, 63.15, 55.08, 51.80, 28.01, 26.92, 26.10, 12.77, 10.43 ppm; IR

(neat): $\tilde{\nu}$ = 3065, 2838, 1588, 1499, 806, 702 cm^{-1}; HR-FAB: *m*/*z*: calcd for $C_{17}H_{22}NO_4$: 304.1645 [*M*−OMe]$^+$; found: 304.1647.

Methyl 6-methoxy-N-*benzyloxycarbonyl-(2*S*)-allylpipecolinate* (***23b***): Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.34 (m, 5H), 6.10–6.00 (m, 1H), 5.45 (s, 1H), 5.17–5.02 (m, 4H), 3.56 (brs, 3H), 3.84 (s, 3H), 3.10–3.04 (m, 1H), 2.54–2.38 (m, 2H), 2.04–1.68 ppm (5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.66, 155.48, 135.85, 135.25, 128.37 (2C), 128.31, 128.15, 128.00, 117.34, 81.96, 67.39, 62.52, 54.96, 51.87, 39.90, 27.82, 25.83, 11.88 ppm; IR (neat): $\tilde{\nu}$ = 3066, 2950, 1576, 1499, 1402, 916, 769, 698 cm^{-1}; HR-FAB: *m*/*z*: calcd for $C_{18}H_{22}NO_4$: 316.1550 [*M*−OMe]$^+$; found: 316.1550.

Methyl 6-methoxy-N-*benzyloxycarbonyl-(2*S*)-(3-propynyl)pipecolinate* (***23c***): Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.19 (m, 5H), 5.45 (brs, 1H), 5.12–5.03 (m, 2H), 3.62 (brd, *J* = 13.2 Hz, 3H), 3.31 (s, 3H), 3.05 (brs, 1H), 2.81 (brs, 1H), 2.43–2.37 (m, 1H), 1.97–1.64 ppm (6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.87, 156.10, 135.20, 128.50 (3C), 128.30 (2C), 82.11, 70.58, 67.69, 64.50, 63.10, 55.13, 52.26, 37.50, 28.63, 25.99, 12.38 ppm; IR (neat): $\tilde{\nu}$ = 3287, 1499, 1402, 1339, 1310, 1296, 1215, 1132, 1080, 918, 700 cm^{-1}; HR-FAB: *m*/*z*: calcd for $C_{18}H_{20}NO_4$: 314.1410 [*M*−OMe]$^+$; found: 314.1411.

Methyl 6-methoxy-N-*methoxycarbonyl-(2*R*)-methylpipecolinate* (***23h***): Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.45–5.39 (m, 1H), 3.72–3.70 (m, 6H), 3.32–3.27 (m, 3H), 2.49–2.41 (m, 0.5H), 2.39–2.30 (m, 0.5H), 1.93–1.78 (m, 5H), 1.60, 1.56 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.14, 174.86 (1C), 156.38, 82.89, 82.27 (1C), 60.35, 60.07 (1C), 54.92, 54.59 (1C), 52.39, 52.29 (1C), 51.96, 51.69 (1C), 33.79, 30.31, 30.15 (1C), 25.37, 13.54, 12.04 ppm (1C); IR (neat): $\tilde{\nu}$ = 2836, 1869, 1686, 1541, 1456, 1051, 1015, 939, 810, 779, 654 cm^{-1}; HR-FAB: *m*/*z*: calcd for $C_{10}H_{16}NO_4$: 214.1094 [*M*−OMe]$^+$; found: 214.1095.

Ethyl 5-methoxy-N-*benzyloxycarbonyl-(2*S*)-methylprolinate* (***32***): Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.31 (m, 5H), 5.36–5.06 (m, 3H), 4.23–3.95 (m, 2H), 3.44 (d, *J* = 4.2 Hz, 1.5H), 3.29 (d, *J* = 9.9 Hz, 1.5H), 2.47–2.36 (m, 1H), 1.95–1.86 (m, 3H), 1.65–1.51 (m, 3H), 1.28–1.07 ppm (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.13, 154.78, 136.10, 128.43, 128.36, 128.10, 128.06, 127.99, 89.67, 88.96 (1C), 67.24, 67.18 (1C), 61.21, 61.01 (1C), 56.01, 55.41 (1C), 37.26, 35.87 (1C), 30.21, 30.06 (1C), 28.14, 27.04 (1C), 22.14, 20.79 (1C), 13.97, 13.89 ppm (1C); IR (neat): $\tilde{\nu}$ = 3651, 2975, 1742, 1539, 1499, 1458, 1353, 1134, 1065, 698 cm^{-1}; HR-FAB: *m*/*z*: calcd for $C_{16}H_{20}NO_4$: 290.1398 [*M*−OMe]$^+$; found: 290.1398.

Ethyl 5-methoxy-N-*benzyloxycarbonyl-(2*S*)-ethylprolinate* (***33***): Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.32 (m, 5H), 5.48–5.08 (m, 3H), 4.20–3.67 (m, 2H), 3.46, 3.40 (s, 1.5H), 3.31, 3.27 (s, 1.5H), 2.46–1.72 (m, 6H), 1.26–1.06 (m, 3H), 0.92–0.78 ppm (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.27, 173.92 (1C), 155.00, 153.56 (1C), 136.24, 135.98 (1C), 129.62, 129.28 (1C), 128.29, 128.22 (1C), 128.00, 127.91 (1C), 127.89, 127.77 (1C), 127.42, 126.68 (1C), 90.56, 89.82 (1C), 69.10, 68.45 (1C), 67.04, 66.80 (1C), 60.94, 56.03, 55.35 (1C), 35.12, 33.54 (1C), 31.43, 30.93 (1C), 28.48, 26.96 (1C), 13.91, 13.81 (1C), 8.27 ppm; IR (neat): $\tilde{\nu}$ = 3649, 2980, 2361, 1732, 1541, 1499, 1456, 1401, 1354, 1204, 1165, 1075, 955, 698 cm^{-1}; HR-FAB: *m*/*z*: calcd for $C_{17}H_{22}NO_4$: 304.1591 [*M*−OMe]$^+$; found: 304.1591.

General procedure for α′-methoxy-group cleavage of α′-methoxy-*N*-acyl-α-alkyl-amino acid esters 20, 23a–g, 32, and 33: Triethylsilane (0.375 mmol) was added to a stirred solution of the substrate (0.25 mmol) in CH_2Cl_2 (5 mL) under nitrogen at −78 °C. The temperature was elevated to 0 °C over 30 min. Methane sulfonic acid (0.30 mmol) was then added dropwise and the mixture was stirred at room temperature for a further 8 min. Water (10 mL) was added and the solution was extracted by using $CHCl_3$ (3×10 mL). The organic layer was dried by using anhydrous magnesium sulfate and filtered. The filtrate was concentrated in vacuo and the concentrate was purified by using silica-gel column chromatography to give *N*-acyl-α-alkyl-amino acid esters **19**, **24a–c**, **24h**, **34**, and **35**.

Compound **24h**[29] is known and the spectroscopic data is available in the literature.

Methyl N-*benzyloxycarbonyl-(2*R*)-methylpipecolinate* (***19***): Compound **19** was prepared from methyl 6-methoxy-*N*-benzyloxycarbonyl-(2*R*)-methylpipecolinate (**20**) according to the general procedure and purified by silica-gel column chromatography (hexane/ethyl acetate 15:1). HPLC analysis of **19** was carried out by using Daicel Chiralcel OJ (0.46 cmØ × 25 cm): *n*-hexane/isopropanol 10:1, λ = 254 nm, flow rate = 0.5 mL min^{-1}, retention time = 17.7 (*R*), 21.6 min (*S*), >99% *ee*; colorless oil; $[\alpha]_D^{30}$ = −16.00 (*c* = 2.50 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.32 (m, 5H), 5.13 (d, *J* = 12.0 Hz, 1H), 5.07 (d, *J* = 12.0 Hz, 1H), 3.94–3.88 (m, 1H), 3.65 (brs, 3H), 3.11–3.04 (m, 1H), 1.93–1.86 (m, 1H), 1.77–1.57 (m, 5H), 1.49 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.09, 156.20, 136.35, 128.37 (3C), 127.96 (2C), 67.21, 60.65, 52.04, 41.29, 34.84 (2C), 23.59, 18.31 ppm; IR (neat): $\tilde{\nu}$ = 2951, 2869, 1962, 1750, 1609, 1588, 1499, 1456, 1406, 1350, 1291, 1200, 1144, 1038, 1003, 889, 855, 826, 777, 737, 700, 608 cm^{-1}; HR-FAB: *m*/*z*: calcd for $C_{16}H_{22}NO_4$: 292.1568 [*M*+H]$^+$; found: 292.1570.

Methyl N-*benzyloxycarbonyl-(2*R*)-ethylpipecolinate* (***24a***): Compound **24a** was prepared from methyl 6-methoxy-*N*-benzyloxycarbonyl-(2*R*)-ethylpipecolinate (**23a**) according to the general procedure and purified by silica-gel column chromatography (hexane/ethyl acetate 15:1). HPLC analysis of **24a** was carried out by using Daicel Chiralcel OJ (0.46 cmØ × 25 cm): *n*-hexane/isopropanol 10:1, λ = 254 nm, flow rate = 0.5 mL min^{-1}, retention time = 13.4 (*R*), 16.1 min (*S*), >99% *ee*; colorless oil; $[\alpha]_D^{32}$ = −5.42 (*c* = 0.50 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 (s, 5H), 5.13 (d, *J* = 12.7 Hz, 1H), 5.07 (d, *J* = 12.7 Hz, 1H), 3.94–3.88 (m, 1H), 3.61 (brs, 3H), 3.18–3.10 (m, 1H), 2.19–2.11 (m, 1H), 1.97–1.52 (m, 7H), 0.91 ppm (t, *J* = 7.32 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.67, 156.26, 128.37 (4C), 127.95 (2C), 67.17, 63.71, 51.87, 41.63 (2C), 31.32 (2C), 18.09, 8.56 ppm; IR (neat): $\tilde{\nu}$ = 2950, 2878, 1779, 1701, 1499, 1456, 1341, 1267, 1194, 1167, 824, 735, 698 cm^{-1}; HR-FAB: *m*/*z*: calcd for $C_{17}H_{24}NO_4$: 306.1719 [*M*+H]$^+$; found: 306.1721.

Methyl N-*benzyloxycarbonyl-(2*S*)-allylpipecolinate* (***24b***): Compound **24b** was prepared from methyl 6-methoxy-*N*-benzyloxycarbonyl-(2*S*)-allylpipecolinate (**23b**) according to the general procedure and purified by silica-gel column chromatography (hexane/ethyl acetate 15:1). HPLC analysis of **24b** was carried out by using Daicel Chiralcel OJ (0.46 cmØ × 25 cm): *n*-hexane/isopropanol 10:1, λ = 254 nm, flow rate = 0.5 mL min^{-1}, retention time = 12.7 (*R*), 14.1 min (*S*), >99% *ee*; colorless oil; $[\alpha]_D^{32}$ = −56.81 (*c* = 1.67 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26 (brs, 5H), 5.84–5.79 (m, 1H), 5.03 (d, *J* = 35 Hz, 2H), 5.00 (d, *J* = 34 Hz, 2H), 3.84 (brs, 1H), 3.55 (brs, 3H), 3.08–3.01 (m, 1H), 2.81–2.76 (m, 1H), 2.59–2.52 (m, 1H), 1.82–1.50 ppm (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.30, 156.12, 136.42, 133.94, 128.36 (3C), 127.95 (2C), 118.25, 67.17, 62.99, 51.96, 41.41, 31.77 (2C), 28.87, 17.72 ppm; IR (neat): $\tilde{\nu}$ = 2950, 2870, 1744, 1709, 1638, 1499, 1453, 1404, 1347, 1266, 1192, 1163, 1136, 1005, 918, 824, 781, 733, 698 cm^{-1}; HR-FAB: *m*/*z*: calcd for $C_{18}H_{24}NO_4$: 318.1709 [*M*+H]$^+$; found: 318.1709.

Methyl N-*benzyloxycarbonyl-(2*S*)-(2-propynl)pipecolinate* (***24c***): Compound **24c** was prepared from methyl 6-methoxy-*N*-benzyloxycarbonyl-(2*S*)-(3-propynyl)pipecolinate (**23c**) according to the general procedure and purified by silica-gel column chromatography (hexane/ethyl acetate 15:1). HPLC analysis of **24c** was carried out by using Daicel Chiralpak AD (0.46 cmØ × 25 cm): *n*-hexane/isopropanol 20:1, λ = 254 nm, flow rate = 0.5 mL min^{-1}, retention time = 25.9 (*S*), 28.4 min (*R*), 75% *ee*; colorless oil; $[\alpha]_D^{32}$ = −50.05 (*c* = 1.25 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.32 (m, 5H), 5.15 (d, *J* = 9.2 Hz, 1H), 5.10 (d, *J* = 9.2 Hz, 1H), 3.92 (brs, 1H), 3.69 (brs, 3H), 3.38–3.31 (m, 1H), 2.81 (d, *J* = 17.08 Hz, 1H), 2.33–2.28 (m, 1H), 1.99–1.98 (m, 1H), 1.81–1.64 ppm (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.47, 155.89, 128.41 (3C), 127.98 (2C), 127.77, 80.01, 70.63, 67.27, 62.21, 52.22, 41.44, 31.37 (2C), 22.10, 17.13 ppm; IR (neat): $\tilde{\nu}$ = 3289, 2951, 2874, 2120, 1744, 1499, 1456, 1412, 1345, 1264, 1194, 1161, 1129, 1063, 980, 777, 700, 652 cm^{-1}; HR-FAB: *m*/*z*: calcd for $C_{18}H_{22}NO_4$: 316.1555 [*M*+H]$^+$; found: 316.1556.

*Methyl (2*R*)-methylpipecolinate (**25**)*: Me_3SiI (2.0 mmol) was added to **24h** (0.5 mmol) in dichloromethane (5 mL), and the solution refluxed at 60 °C for 3 h. NaOH (1 N, 5 mL) was added to achieve a pH value of 10, then saturated $Na_2S_2O_3$ (4 mL) was added and the mixture was extracted in chloroform (3×10 mL). The organic layer was dried by using anhy-

drous magnesium sulfate and filtered. The filtrate was concentrated in vacuo to yield compound **25** (1.14 mmol).

By starting from **19** (0.5 mmol) in methanol (5 mL), deprotection was achieved by using Pd/C (5%) and hydrogen (1 atm.) for 6 h. The solution was filtered under pressure by using Celite (Celite 545RVS, Nacalai tesque), and the filtrate concentrated to yield compound **25** (1.64 mmol).

The *ee* value was determined to be >99% by gas chromatography (TCI Chemical Industries, Chiraldex B-DA, 0.25 mm (i.d)×30 m×0.25 μm) at a constant temperature of 120°C and a retention time of 10.33 min (*R*). Colorless oil; $[\alpha]_D^{21}=-41.86$ ($c=1.0$ in $CHCl_3$); lit.:[14] (*S*)-**25**; 95% *ee*; $[\alpha]_D^{20}=+8.0$ ($c=5.0$ in $CHCl_3$).

Ethyl N-*benzyloxycarbonyl-(2*S*)-methylprolinate* (***34***): Compound **34** was prepared from ethyl 5-methoxy-*N*-benzyloxycarbonyl-(2*S*)-methylprolinate (**32**) according to the general procedure and purified by silica-gel column chromatography (hexane/ethyl acetate 15:1). HPLC analysis of **34** was carried out by using Daicel Chiralpak AD (0.46 cmØ×25 cm): *n*-hexane/isopropanol 30:1, $\lambda=254$ nm, flow rate $=0.5$ mL min^{-1}, retention time $=24.4$ (*R*), 27.8 min (*S*), 72% *ee*; colorless oil; $[\alpha]_D^{24}=-11.76$ ($c=1.0$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.35$–7.32 (m, 5H), 5.20–5.05 (m, 2H), 4.17 (q, $J=7.2$ Hz, 1H), 4.00–3.87 (m, 1H), 3.69–3.56 (m, 2H), 2.21–2.15 (m, 1H), 1.99–1.85 (m, 3H), 1.61, 1.54 (s, 3H), 1.21, 1.08 ppm (2t, $J=7.2$, 7.2H, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=174.33$, 174.14 (1C), 154.21, 154.12 (1C), 136.92, 136.36 (1C), 128.31, 127.93, 127.84, 127.74, 127.61, 66.86, 66.43 (1C), 65.62, 64.89 (1C), 61.03, 60.99 (1C), 48.46, 47.68 (1C), 40.40, 36.13 (1C), 23.21, 23.08 (1C), 22.68, 22.01 (1C), 14.01, 13.90 ppm (1C); IR (neat): $\tilde{\nu}=3065$, 2982, 2878, 1748, 1609, 1588, 1541, 1499, 1420, 1362, 1184, 1140, 1073, 914, 864, 770, 700 cm^{-1}; HR-FAB: *m/z*: calcd for $C_{16}H_{22}NO_4$: 292.1545 $[M+H]^+$; found: 292.1544.

Ethyl N-*benzyloxycarbonyl-(2*S*)-ethylprolinate* (***35***): Compound **35** was prepared from ethyl 5-methoxy-*N*-benzyloxycarbonyl-(2*S*)-ethylprolinate (**33**) according to the general procedure and purified by silica-gel column chromatography (hexane/ethyl acetate 15:1). HPLC analysis of **35** was carried out by using Daicel Chiralpak AD (0.46 cmØ×25 cm): *n*-hexane/isopropanol 10:1, $\lambda=254$ nm, flow rate $=0.5$ mL min^{-1}, retention time $=$ 24.3 (*R*), 28.3 min (*S*), 64% *ee*; colorless oil, $[\alpha]_D^{24}=-16.41$ ($c=1.25$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.54$–7.45 (m, 5H), 5.39–5.21 (m, 2H), 4.39–4.32 (q, $J=7.2$ Hz, 1H), 4.24–3.90 (m, 2H), 3.73–3.64 (m, 1H), 2.58, 2.38 (2sexlet, 7.2, 7.2 Hz, 1H), 2.30–2.00 (m, 5H), 1.40, 1.29 (2t, $J=7.2$, 7.2 Hz, 3H), 1.05, 1.03 ppm (2t, $J=7.5$, 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=174.66$, 174.44 (1C), 154.56, 154.26 (1C), 137.00, 136.38 (1C), 128.32, 127.95, 127.86, 127.73, 127.52, 68.90, 68.05 (1C), 66.92, 66.44 (1C), 60.93, 60.89 (1C), 49.31, 48.50 (1C), 36.87, 35.36 (1C), 27.42, 26.27 (1C), 23.13, 22.69 (1C), 14.03, 13.95 (1C), 7.84, 7.68 ppm; IR (neat): $\tilde{\nu}=3034$, 2979, 2880, 1740, 1713, 1499, 1456, 1406, 1356, 1273, 1173, 1075, 1028, 698 cm^{-1}; HR-FAB: *m/z*: calcd for $C_{17}H_{24}NO_4$: 306.1701 $[M+H]^+$; found: 306.1700.

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